

CRYSTAL STRUCTURE OF TWO POLYMORPHS OF TMC125 (ETRAVIRINE, INTELENCE) FROM SINGLE CRYSTAL AND X-RAY POWDER DIFFRACTION DATA

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Single crystal X-ray diffraction is the ideal technique for determining the three-dimensional structure of organic compounds in the crystalline state. X-ray Powder diffraction (XRPD) techniques have been traditionally used for identification and quantification of polycrystalline material. The information contained in a powder diffraction pattern is intrinsically less than that obtained from a single crystal, as the three-dimensional intensity distribution is compressed to one dimension.

Unfortunately, the necessary prerequisite to obtain single crystals suitable for X-ray diffraction analysis is not always met for all compounds and some materials are only available as polycrystalline powders. Methods have been developed to solve organic molecular structures from powder data by modeling the structure in direct space (global optimization) using, among others, Monte Carlo simulated annealing (SA). TMC125 (Etravirine, Intelence) is a non-nucleoside reverse transcriptase inhibitor used for the treatment of HIV. The crystal structure of TMC125 form I has been determined using single crystal X-ray diffraction. However, the crystal structure of the polymorphic form II was unknown and not possible to be solved using single crystal diffraction. The crystal structure of TMC125 form II has been solved using conventional XRPD data in combination with SA and whole profile pattern matching, and refined using the Rietveld method. Both polymorphs share very similar crystal structures, as reflected in the similar unit cell volume. The conformation of the TMC125 molecules in both crystalline forms is very similar, as well as the hydrogen-bonding pattern. The calculated XRPD spectra, after Rietveld refinement, can be used as reference for identification of TMC125 form II in possible polymorphic mixtures. This also resolves the issue of similarities in the powder diffractograms of both polymorphs when comparing them.